Case Report

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GENTIAN VIOLET: RE-EXPLORING IT'S POTENTIALS IN ORAL ULCERS: A CASE SERIES

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ABSTRACT:

Gentian or Crystal violet, an atriarylmethane dye used as a histological stain and in Gram's staining of bacteria, has antibacterial, antifungal and antihelmintic properties and was a popular topical antiseptic. It's medical usage has been largely superseded by modern antimicrobials and other antiseptics, although it is still listed by the World Health Organization as a topical antiseptic agent. It has been frequently used in the management of various dermatological lesions like fungal skin infections, vulvovaginal candidiasis (vaginal thrush), bacterial skin infections such as infected eczema, boils, and chronic (long-standing) leg ulcers. Gentian violet may also be active against Methicillin-resistant Staphylococcus aureus (MRSA) and oral lesions like oral thrush and a variety of oral ulcers. However, there is hardly any scientific clinical evidence available to support its effectiveness in the management of oral ulcers except for few reviews and case reports. Here, we are sharing our clinical experience with it in the management of 40 cases of oral ulcers, where the results were encouraging.

Key words: Oral ulcers, Gentian violet, Management of oral ulcers.

INTRODUCTION

An ulcer is a breach in the continuity of the epithelium, which typically exposes nerve endings in the underlying lamina propria, resulting in pain or soreness. Oral ulcer is a common disease we come across, with an estimated 4% world-wide point prevalence. The most common oral ulcer is traumatic ulcer followed by recurrent aphthous ulcers. The etiology for oral ulcers is multifactorial like trauma, infections caused by bacteria, virus and fungi, immunologically mediated diseases, allergy, nutritional deficiency, blood dyscrasias, malignancy etc.[1]

Although the exact microbial cause of oral ulcers is unknown but the microorganisms suggested to cause infection in oral ulcers are gram positive oral (viridans) streptococci like S. mitis, S. sanguis, S. oralis and gram negative bacteria H. pylori.[2]

An oral ulcer on an average takes five to seven days to heal. Common symptoms include pain, burning sensation, difficulty in eating and chewing. The management

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of oral ulcer is usually complicated due to presence of saliva; persistent moist environment, food, food debris, water, oral microorganisms etc.[3]The treatment begins with identification of the underlying cause; and usually when the cause is removed it takes three to four days to heal.

The goal of treatment is to alleviate symptoms, accelerate healing time and prevent recurrence. Current treatments mainly used are topical agents such as anesthetics, analgesics, antimicrobials, steroids depending on etiology and type of ulcers. Some systemic agents like steroids, steroid sparing agents and immunomodulators like azathioprin, cyclosporine, thalidomide, levamisole, cyclophosphamide, dapsone, colchicines and pentoxiphylline may be reserved for severe and refractory cases as these medications are associated with many adverse effects when compared to topical medications.[1]

Crystal violet or Gentian violet belongs to di- and triaminophenylmethanes class of dyes .This dye is used as a histological stain and in Gram's method of classifying bacteria. Gentian violet has shown to have antibacterial, antifungal and antihelminthic properties [3] and has been used as an antiseptic agent since early 19th century. It was widely used in World War II as a topical antiseptic agent on war wounds.[4] Further it has been being used in atopic eczema, pressure sores, decubitus ulcers, pyodermas, oropharyngeal and vaginal candidiasis, HIV associated oral hairy leukoplakia, ulcerated infantile hemangiomas, cutaneous melanoma metastasis, transgredientpachyonychia congenital, tinea infestation like athlete's foot and ringworm and impetigo.[4,5] The medical use of the dye has been largely superseded by more modern drugs, although it is still listed by the World Health Organisation.[6,7]

Apart from being an antiseptic agent Gentian violet also acts as a surface astringent and coagulates the proteins on the ulcer surface.[8] Thus, it coats the surface of the ulcer and protects it from hostile oral environment and accelerates healing of ulcer. Therefore, by virtue of these properties usage of gentian violet is advocated in the management of oral ulcers and few studies have reported quoting its effectiveness in management ulcers on other parts of the body. [9,10] We used this antiseptic dye in the management of few cases oral ulcers and share our clinical experience.

METHODS AND MATERIALS:

A total of 40 patients, 22 males and 18 females, in the age range of 10 to 70 years were treated in the outpatient department of our institute between January 15th, 2014 andJune 1st, 2014 after obtaining informed consent from the patient. Patients of any age and either sex presenting with oral ulcers regardless of the etiology except malignant ulcers and ulcers secondary to systemic causes were treated. Patient having known hypersensitivity to the dye, ulcers due to systemic diseases or malignancies were not considered for the dye application.

Patient's demographic data, history of illness and clinical findings were entered in a structured proforma. Elective coronoplasty of the offending tooth, wherever required was done prior to application of medication. After evaluation of the oral ulcers patients were made to rinse mouth thoroughly with water to get rid of any debris present over the ulcer and a drop of gentian violet was applied topically directly above the ulcer with the help of a cotton pellet and tweezer. Patients were refrained from eating, drinking or rinsing mouth for at least 30 minutes post application. Patients were recalled on the 3rd day for evaluation and medication was re-applied if needed and reviewed again on the 6th day. The parameters evaluated were pain associated with ulcers on VAS, size of ulcers in mm, morbidity in percentage and effect on the quality of life in percentage.

The data collected from each patient was entered in a master chart, tabulated and subjected to statistical analysis using 't-test' and 'Wilcoxon signed ranks' tests.

RESULTS:

A total of 40 patients, 22 males and 18 females, in the age range of 10 to 70 years presenting with a total of 51 ulcers were initially treated. Out of these, 27 patients (16 males and 11 females) came for regular follow up and three could be followed up only telephonically, while remaining 10 were lost to follow up. Those contacted telephonically on the fourth day reported relief from ulcer and pain. The data of 27 patients with regular follow up was used for statistical analysis (Table 1).

In these 27 patients, a total of 38 ulcers were evaluated, out of which 24 had healed by 3rd day and remaining 14 had healed on 2nd follow up by the 6th day after second application of the drug (Table 2).

There was 89.41% mean reduction in size of ulcer, 37% reduction in mean morbidity and 41.22% mean improvement in the quality of life on the third day. Pain on VAS showed significant improvement with mean value reducing from 21.48 to 4.54 post treatment at first follow up and being zero at second follow up. (Table 3)

DISCUSSION

Oral ulcer is a common disease we come across, presenting with a 4% world-wide point prevalence and a multifactorial etiology.

Oral ulcers lead to significant morbidity due to pain, burning sensation, difficulty in eating, chewing and speech. The management is difficult due to presence of saliva; a moist environment, presence of food, bacteria and debris. Usually they are self healing due to high vascularity of the mucosa and heal in 5-7 days if the etiology is taken care of.

However, apart from removing etiology wherever possible, the goal of management is to accelerate healing time, decrease pain, reduce ulcer size and erythema. Many therapies both topical and systemic have been suggested to treat the disease with varying success rates. Current treatments mainly used are

topical agents such as anesthetics, analgesics, antimicrobials, steroids depending on etiology and type of ulcers. These agents provide localized action without systemic adverse effects. Some systemic agents like steroids, steroid sparing agents and immunomodulators like azathioprin, cyclosporine, thalidomide, levamisole, cyclophosphamide, dapsone, colchicines and pentoxiphylline may be reserved for severe and refractory cases as these medications are associated with many adverse effects when compared to topical medications.[1]

Gentian violet, a forgotten topical antiseptic, is being sporadically and successfully used in the management of these ulcers by many clinicians and dentist but there is lack of sufficient accredited scientific literature supporting its efficacy. The aim of the present study was to re-explore the efficacy of this antiseptic dye in the management of oral ulcers and to evaluate whether the sporadic claims made about the so called healing properties can be proved.

Interestingly on a positive note the findings of our study were quite encouraging as we found good response to topical gentian violet in the management of oral ulcers. Out of 41 ulcers in 30 patients, 27 had healed by the end of third day of application or probably even prior to this. The remaining 14 ulcers were healed when patients were re-evaluated at 6th day; these ulcers too probably may have had healed prior to the 6th day. Ten patients were lost to follow up, which may be due to the fact that our institute is little far from the city and possibly patients were relieved of the pain. Three patients who we could contact telephonically on 3rd day informed that their ulcer had got healed and they were free from pain. These 13 patients were not considered for the statistical analysis. Also, there was a significant reduction in the size of the ulcer, pain and morbidity associated with the ulcer after application of the dye. Thus it can be concluded that topical application of gentian violet on intraoral ulcers not only results in faster healing time but also in significant reduction of pain and improvement in quality of life.

There is little scientific literature available quoting gentian violet in the management of oral ulcers, hence we are not able to compare our results directly with that of other studies, however, the findings of our study are quite encouraging.

By means of it's astringent, antiseptic, protective and healing properties gentian violet can be suggested in the management of oral ulcers. The mean healing time with topical gentian violet in our study was 4.10 days which was near or better than the commonly prescribed medications for oral ulcers (Table-4).Gentian violet has no reported potential adverse-effects when used topically in such small quantities and hence is a cheaper and safer alternative to other topically applied medications like corticosteroids and can be recommended for almost all population groups.

Most commonly prescribed medications for the management of oral ulcers include local anesthetic ointments, topical anti-inflammatory drugs and antiseptics. Chlorhexidinegiuconate both as a mouthwash and gel preparations has been reported to produce significant reduction in the duration and discomfort of aphthous ulcers. The broad spectrum antibacterial effect of chlorhexidinegluconate is the major factor which accounts for the reduction in duration and severity of ulceration in recurrent oral ulceration.[11] Bacterial colonization of the wound surface in the mouth always tends to occur and there will be a tendency for delayed healing as a result of increased inflammation and granulation tissue formation, presumably with increased pain.[12] It is probable that chlorhexidine negates this bacterial colonization at least to some degree and this is consistent with the findings that anti-bacterial agents, including chlorhexidine used on healing surgical wounds, reduce the incidence of pain and facilitate healing.[11] Chlorhexidine is generally used as a 0.2% w/w mouth rinse, but the 0.10% w/w mouthwash or 1% gel can also be beneficial.[13] The average duration of healing with chlorhexidine assessed in different studies was in near concordance with study done by Addy M, Carpenter R, Roberts WR, 1976 with 1% Chlorhexidine gel was 4.8 days(mean)[11] while it was superior to study done by Hunter L, Addy M, 1987 with 0.2% Chlorhexidine mouthwash a healing time of 5.02 days (mean) [14]. The adverse drug reactions included nausea, altered taste sensation, and discoloration of the teeth and mucosa on prolonged use.[15]

Another commonly prescribed or rather misused and abused medication for oral ulcers is topical anesthetic agents. These agents include different formulations and different active compounds that provide a symptomatic relief by virtue of their anesthetic properties and also cover the lesion and provide a barrier when formulated with orabase or sucralfate as base. Some of these are also mouthwashes containing benzydamine or diphenhydramine. Most are available in gel form containing local anesthesics like benzocaine in varying percentages (6.4% to 20%), lidocaine (2% to 5%),benzalkonium chloride 0.01% or choline salicylate 8.7%.[16]Further it needs to be applied repeatedly for better results, however gentian violet application even once in office provides better or equivalent results. Probably if applied daily or may be twice a day may fetch even faster healing.

Descroix V in a randomized, double-blind, placebo-controlled, parallel-group trial concluded that topical application of a 1% lidocaine cream for 1 minute to an aphthous ulcer produces a significant reduction in pain intensity 3 minutes after application. The lidocaine cream does not elicit any side effects. Thus, a benefit/risk ratio positive for the application of a 1% lidocaine cream in the symptomatic treatment of acute pain resulting from traumatic or aphthous lesions of the oral mucosa. The pain decreased by

approximately 50% on average.[16] However this painrelief is transient and there is no acceleration of the healing time. So patient has to apply multiple times in a day for consistent pain relief.

Another antimicrobial agent commonly prescribed is Tetracycline. Tetracyclines are broad spectrum antimicrobials with bacteriostatic activity and are effective against large number of gram positive and gram negative bacteria. Tetracyclines when used topically are reported to reduce pain and duration of ulcers as a result of the less heavily colonized environment.[13] Graykowski EA, Kingman A, 1978 conducted a double-blind trial with topical 5% Tetracycline rinse in recurrent aphthous ulceration and recorded a mean healing time of 5.46 days.[17] Here too the limitations are same as seen in case of chlorhexidine along with the risk of hypersensitivity reactions, growth of resistant organisms and loss of symbiotic microflora.[13]

Topical immunmodulators including corticosteroids too are found to be effective in the management of oral ulcers and are one of the most prescribed agents. They are intended to limit the inflammatory process associated with the formation of ulcers and suppress the process of autoimmunity. The anti-inflammatory action of corticosteroids modifies, in a minor way, the progress of the inflammation at all stages and to some extent reduces the discomfort experienced. The second effect of steroids is the specific blocking effect of the T lymphocyte-epithelial cell interaction. Since the concentration of sensitized lymphocytes occurs before and during the early stages of oral ulceration, it follows that the drugs exert their maximum effect at this time.[13]

Commonly prescribed topical steroids are hydrocortisone hemisuccinate (as pellets of 2.5 mg) and triamcinolone acetonide 0.1% in orabase. Other agents include: dexamethasone rinse 0.05mg/ml, clobetasol ointment 0.05% in orabase, flucinonide ointment 0.05% in orabase. orabase or other adherent base is used in formulation provides a protective local coating for the ulcer. Early initiation (within 72 hours) of this treatment may result in a more rapid response. There is little risk of adrenal suppression provided that the recommended dose (four times daily) is adhered to.[18]

Merchant HW, Gangarosa LP, Glassman AB et al, 1978 investigated healing time of < 6 days with topical 0.025% betamethasone benzoate gel.[19] Prolonged use of potent topical corticosteroids carries a risk of systemic absorption and associated adverse effects like bad taste, nausea, dry mouth, mucosal atrophy; delayed healing, allergy and may also predispose to secondary oral candidosis.[13]

Amlexanox is a topical anti-inflammatory, anti-allergic drug. It has been developed as a 5% topical oral paste for the treatment of patients with oral ulcers. It inhibit the formation and release of histamine and leukotrienes from mast cells, neutrophils, and mononuclear cells, possibly through increasing intracellular c-

AMP content in inflammatory cells, and a membrane-stabilizing effect or inhibition of calcium influx. The paste is applied to ulcers two to four times a day. Meng W et al, 2009 in a randomized, blinded, placebo controlled, parallel, multicentre, clinical design concluded that amlexanox group had a statistically significant higher "improvement" rate 66.67% vs 43.81% in placebo control group.[20]

Levamisole is an immunomodulatory drug which makes it useful in controlling oral ulcers.Levamisole has demonstrated the ability to normalize the CD4+ cell/CD8+ cell ratio and improve symptoms in RAU patients. Correction of T-suppressor cell deficiency may reduce the inflammatory response resulting from cellular immunity and promote resolution of aphthae.[15]The major adverse effects associated with levamisole were nausea, hyperosmia, dysgeusia, and agranulocytosis.[2] Olson JA, Silverman S, 1978 conducted a double-blind study in 48 patients of recurrent aphthous stomatitis with levamisole dosage of 150 mg/day × 3 days every week at first sign of ulcers. 65% of patients reporting moderately or markedly reduced pain against 28% in placebo control group.[21]

Diaminodiphenylsulphone (Dapsone) a widely used drug in the long-term treatment of leprosy and some dermatologic conditions have been tried with limited success in the management of major aphthae. Dapsone is given 100mg orally in divided doses and may be increased at the rate of 50mg/day per week to a maximum of 300mg/day. Dapsone is a potentially toxic drug, can precipitate hemolyticanemia, hence, the patients should be monitored for hemolysis, methemoglobinemia, anemia and agranulocytosis.[13] Sharquie et al, 2002 found that dapsone was effective at decreasing the number, duration of oral ulcers in 20 patients. [22]

However, larger controlled or blinded studies using a placebo or a comparative arm medication is advocated preferably in a long term clinical trial to substantiate the results reported from the present case series.

CONCLUSION

The primary goals of therapy for oral ulcers are relief of pain, reduction of ulcer duration, and restoration of normal oral function. Localized topical regimens can achieve the primary goals and are considered to be the standard treatment of oral ulcers. In the present prospective study gentian violet was found as an effective potential drug in management of oral ulcers. Hence its potentials should be re-explored since it is easily available, cost effective, safe and shows good efficacy.

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TABLES:

Table-1: **Age And Sex Distribution**

Sex	Age range(years)	Mean age(years)
MALE (16)	**10-70**	**33.87**
FEMALE (11)	**20-40**	**28.72**
TOTAL (27)	**10-70**	**31.77**

Table-2 :**Treatment Summary**

Criteria	Number of ulcer/total numbers of ulcers
Number of patients with 50% relief in ulcer on 3rd day	14/38
Number of patients with 100% relief in ulcer on 3rd day	24/38
Number of patients with 50% healing in ulcer on 3rd day	14/38
Number of patients with 100% healing in ulcer on 3rd day	24/38
Number of patients with 100% relief in ulcer on 3rd day	38/38
Number of patients with 100% healing in ulcer on 3rd day	38/38

Table-3: **Criteria Evaluated Pre- Treatment And Post- Treatment**

Criteria evaluated	Pre-treatment	3rd day Post-treatment	6th day Post- treatment	p-value
Size of the ulcer (in mm; mean±SD)	0.2504 ±0.6593	0.0265 ±0.0516	0	0.0348 (S)
Percentage morbidity (mean±SD)	41.67 ±19.79	4.67 ±7.43	0	<0.0001 (S)
Effect on the quality of life (mean±SD)	50.750 ±13.79	9.525 ±13.79	0	<0.0001 (S)
Pain on VAS	21.48	4.54	0	<0.0001 (S)

Table-4: **Healing Time Of Some Commonly Prescribed Medications.**

	Healing time
Addy M, Carpenter R, Roberts WR, 1976.[11] 1% Chlorhexidine gel	Mean = 4.8 days
Hunter L, Addy M, 1987.[14] 0.2% Chlorhexidine mouthwash	Mean = 5.02 days
Graykowski EA, Kingman A,1978.[17] 5% Tetracycline rinse	Mean = 5.46 days
Merchant HW, Gangarosa LP, Glassman AB et al, 1978.[19] 0.025% Betamethasone benzoate gel	< 6 days
Mostafa A A E and Ibrahem A EM, 2009.[23] Topical application of Quercetin	4 to 7 days